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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/566,094	10/03/2006	Ramon Merce Vidal	284057US0PCT	9552

22850 7590 11/05/2010

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ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
11/05/2010	ELECTRONIC

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/566,094
Filing Date: October 03, 2006
Appellant(s): MERCE VIDAL ET AL.

Vincent K. Shier
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 4, 2010 appealing from the Office action mailed October 1, 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after the previous non-final rejection contained in the brief is correct. No amendments have been made after the Final Rejection mailed October 1, 2009.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

No rejections are withdrawn herein and no new grounds of rejection are presented herein.

(7) Claims Appendix

The copy of appealed claims 1-14, 18-19, 46-47, 74-93 that appears on pages 1-17 of the Claims Appendix to the appellant's brief is correct.

(8) Evidence Relied Upon

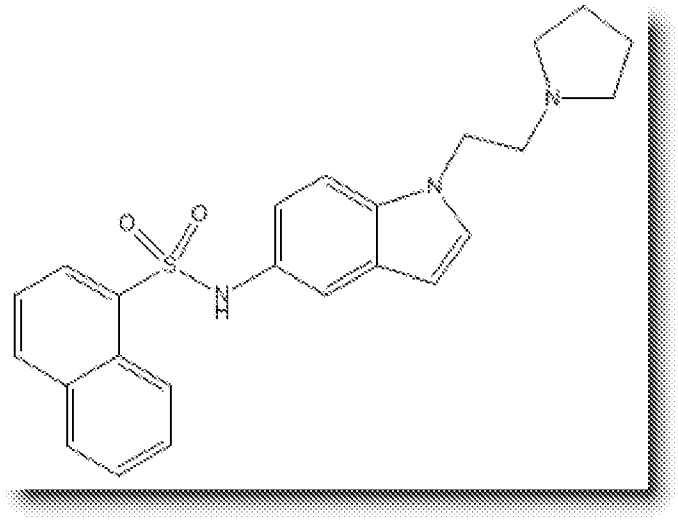
WO 2003/042175	MERCE-VIDAL ET AL	5-2003
WO 2002/060871	FILLA ET AL	8-2002

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

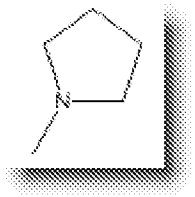
1. **Claims 1-14, 18, 19, 46, 47, 74-82, 84-90, 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over *MERCE-VIDAL ET AL* (WO 2003/042175) and *FILLA ET AL* (WO 2002/060871).**

2. The instant invention is drawn to compounds of formula (Ia) which are disclosed by the Specification as 5-HT_6 modulators and which encompasses the following specific compound



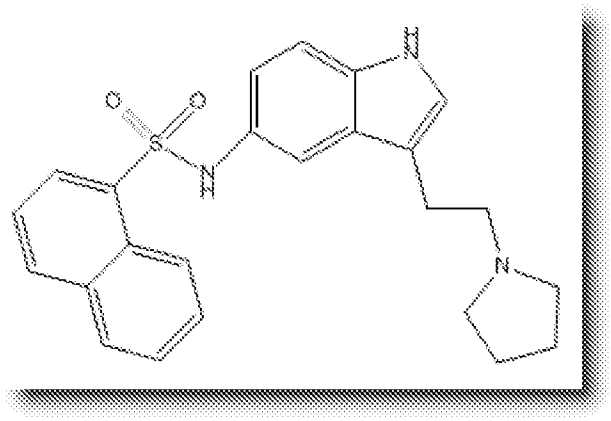
wherein (in formula (Ia)) R1 is NR^8R^9 and

R^8R^9 together with the bridging nitrogen atom form a saturated heterocyclic ring, specifically



; R2-R7 are hydrogen; and A is a polycyclic aromatic ring system, wherein the rings are 6 membered. Specifically, the above compound is disclosed in the instant Specification as N-[1-(2-pyrrolidine-1-yl-ethyl)-1H-indole-5-yl]-naphthalene-1-sulfonamide (Page 78, Example 17) and the compound reads on claims 1-8 and 76-82.

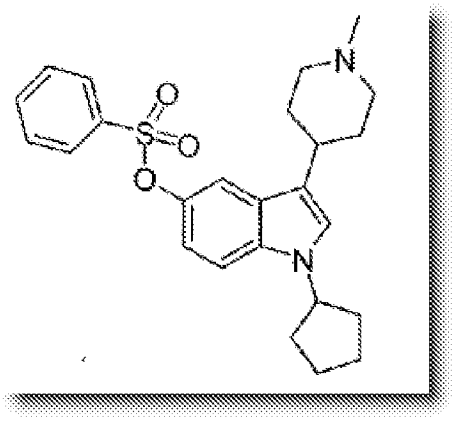
3. *Merce-Vidal et al* teach compounds which are disclosed as 5-HT_6 modulators. In particular, *Merce-Vidal et al* disclose the compound N-{3-[2-(pyrrolidin-1-yl)-ethyl]-1H-indole-5-yl}-naphthalene-1-sulfonamide, having the following structure:



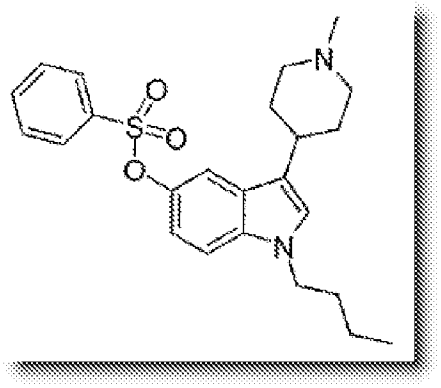
(Page 6, Example 45). Accordingly, the **only** difference between the instant species and that taught by *Merce-Vidal et al* is the placement of -$(CH_2)_n$-R_1 (wherein -$(CH_2)_n$-R_1 in the instant invention and in *Merce-Vidal et al* are the same) on the indole core. Since the compounds are positional isomers of each other, any subtle differences between the compound taught by *Merce-Vidal et al* and the instantly claimed species is *prima facie* obvious in view of *In re Wilder*, 563 F.2d 457 (CCPA 1977); as stated by MPEP

2144.09: "[c]ompounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus) or homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by $-CH_2-$ groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977).

4. Furthermore, the person of ordinary skill in the art at the time the invention was made would have found it obvious to substitute the indole ring at position 1 in view of *Filla et al* which teach 5-HT_6 modulators which are substituted at position 1 of their indole ring. Specifically, *Filla et al* teach the following compounds:



(Page 67, Example 28) and

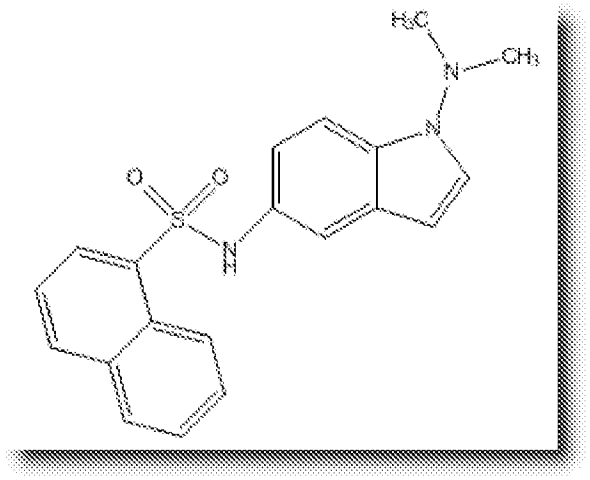


(Page 68, Example 29). Thus, at minimum, *Filla et al* indicates that substitution of the indole core at position 1 does not disrupt the compound's activity as a 5-HT_6 modulator. Accordingly, the skilled artisan seeking to ring-

walk the substituent taught by *Merce-Vidal et al* to a different position on the indole core (to form a position isomer in view of *In re Wilder*) would have reasonably predicted that position 1 of the indole core would be capable of supporting a similar substituent and maintaining activity as a 5-HT_6 modulator in view of *Filla et al*. That is, the skilled artisan - who would ordinarily contemplate making isomers of the compound taught by *Merce-Vidal et al* to try to obtain compounds with improved properties - would consider ring-walking the moiety taught by *Merce-Vidal et al* to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT_6 modulators and possibly possess improved properties.

5. Thus, claim 1-8 and 76-82 are rejected as *prima facie* obvious under 35 U.S.C. 103(a).

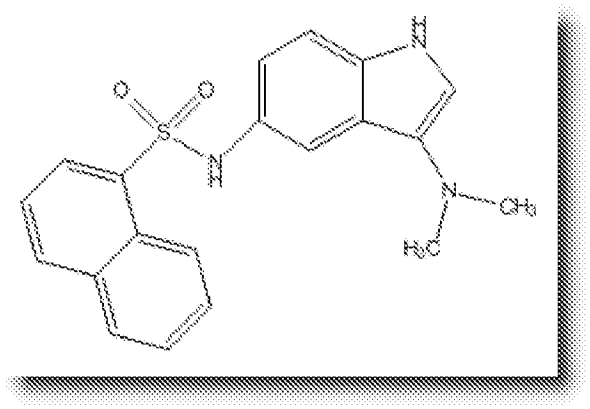
6. Instant claim 9 is drawn to compounds of formula (Ib) which are disclosed by the Specification as 5-HT_6 modulators and which encompasses the following specific compound



wherein R1 is NR^8R^9 and R^8 and R^9 are each CH_3; R2-R7 are hydrogen; and A is a polycyclic aromatic ring system, wherein the rings are 6 membered. Specifically, the above compound is disclosed in the instant Specification as N-[1-

(2-dimethylaminoethyl)-1H-indole-5-yl]-naphthalene-1-sulfonamide (claim 14, Example 3) and the compound reads on claims 9-14 and 86-90.

7. *Merce-Vidal et al* teach compounds which are disclosed as 5-HT_6 modulators. In particular, *Merce-Vidal et al* disclose the compound N-[3-(2-dimethylaminoethyl)-1H-indole-5-yl]-naphthalene-1-sulfonamide (Page 5, Line 3, Example 8) having the following structure:



.

8. Accordingly, the only difference between the instant specie and that taught by *Merce-Vidal et al* is the placement of instant -$(CH_2)_n$-R_1 (wherein -$(CH_2)_n$-R_1 are the same) on the indole core. Since the compounds are positional isomers of each other, any subtle differences between the compound taught by *Merce-Vidal et al* and the instantly claimed species is *prima facie* obvious in view of *In re Wilder*, 563 F.2d 457 (CCPA 1977) for the same reasons discussed above.

9. Furthermore, as discussed above, *Filla et al* teach 5-HT_6 modulators containing the same instant core substituted at position 1 of the indole ring. Accordingly, for the same reasons discussed above, one of ordinary skill in the art would have been motivated to take the -$(CH_2)_n$-R_1 group or similar variants, and place it at various positions on the indole ring (and, in particular, at position 1) to provide 5-HT_6 modulators with a reasonable expectation of success.

10. Thus, claims 9-14 and 86-90 are also rejected as *prima facie* obvious under 35 U.S.C. 103(a).

11. Claims 18 and 46 and drawn to medicaments including the compound of claim 1 or claim 9, respectively, and optionally at least one or more pharmacologically acceptable excipients. *Merce-Vidal et al* specifically teach "pharmaceutical compositions that comprise… an acceptable pharmaceutical excipient" (Page 11, Lines 6-8).

12. Accordingly, claims 18 and 46 are also rejected.

13. Claims 19 and 47 are drawn to the medicaments of claims 18 and 46, respectively, for the treatment of various conditions including, for example, disorders of the central nervous system. *Merce-Vidal et al* specifically teach "a medicament… useful for preventing or treating various disorders of the Central Nervous System" (Page 11, Lines 11-12). Although *Merce-Vidal et al* do not specifically teach that the disclosed medicaments are useful for treating, for example, Alzheimer's disease, as recited by instant claims 92 and 93, Applicant is advised that use limitations within product claims do not carry patentable weight unless the recitation of the intended use of the claimed invention results in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In the instant case, there is nothing to suggest that the *prima facie* obvious compounds taught by *Merce-Vidal et al* in view of *In re Wilder* and *Filla et al* would not be capable of treating Alzheimer's disease. Indeed, *Merce-Vidal et al* specifically disclose that the taught compounds can be used to treat "cognitive memory disorders and senile dementia process, and other dementias in which predominates a cognition deficit" (Page 11, Lines 12-14). Thus, it is asserted

that the *prime facie* compounds necessarily treat Alzheimer's disease, absent evidence to the contrary. As stated in *In re Best, Bolton, and Shaw*, "Where… the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product" 195 USPQ 430, 433, 562 F2d 1252 (CCPA 1977). See also *In re Fitzgerald* 205 USPQ 594, 597, 619 F2d 67 (CCPA 1980): the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on."

14. Accordingly, claims 19, 47 and 92-93 are also rejected.

15. Instant claims 74 and 84 are drawn to compounds according to claims 1 and 9, respectively, wherein the compound is in the form of a physiologically acceptable salt thereof. As disclosed by *Merce-Vidal et al*, the "present invention also relates to the physiologically acceptable salts of the compounds" (Page 6, Lines 33-34).

16. Accordingly, claims 74 and 84 are also rejected.

17. Instant claims 75 and 85 are drawn to compounds according to claims 1 and 9, respectively, wherein the compound is in the form of its enantiomers or diastereoisomers or in the form of a mixture of at least two of its enantiomers and/or diastereoisomers. Since *Merce-Vidal et al* do not specifically teach compounds in the forms of enantiomers or diastereomers, it is understood and would have been obvious to a person of ordinary skill in the art at the time the invention was made that the compounds taught by *Merce-Vidal et al* are drawn to their racemic form. However, as drafted, claims 75 and 85, which recite compounds in the form of a mixture

of at least two of its enantiomers, encompass the racemic compound, which is in the form of a mixture of at least two of its enantiomers.

18. Accordingly, claims 75 and 85 are also rejected.

(10) Response to Argument

Appellant's arguments have been fully considered but are not persuasive. Appellant first argues that "the Court of Appeals in the Federal Circuit clearly state in *Takeda Chemical Industries Ltd. V. Alphapharm Pty, Ltd.*, 83 USPQ2d 1169 (Fed. Cir. 2007) that in order to find a prima facie case of unpatentability, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required" (Brief, Page 7) and that it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish obviousness *prima facie* of a new claimed compound (Brief, Page 7). Yet, as discussed above, the prior suggests the specific molecular modifications necessary to achieve the claimed invention in order to provide similar compounds having similar activity. In particular, *Merce-Vidal et al* teach structurally and functionally related compounds which differ from the instantly claimed compounds in the placement of an identical moiety on an identical core. *In re Wilder* teaches that: "[c]ompounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus)… are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. And *Filla et al* motivate ring walking of the moiety in the compound taught by *Merce-Vidal et al* (to form a position isomer in view of *In re Wilder*) specifically to position 1 of the indole core, to results in the instantly claimed compounds.

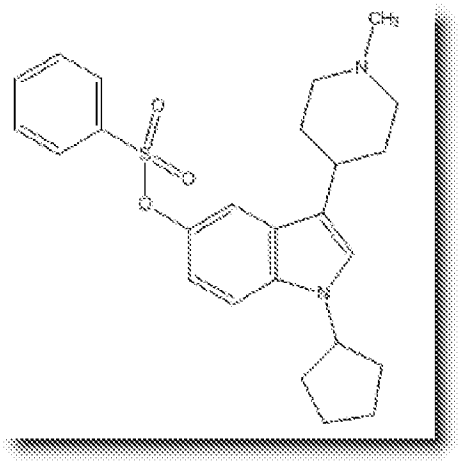
Applicant further argues that *Merce-Vidal et al* "provides no hint as to moving the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring without losing affinity for the 5-HT_6 receptor. Neither would the skilled person have been motivated to change the $-(CH_2)_n-R^2$ moiety of *Merce-Vidal et al* to position 1 in view of the teaching of *Filla et al*" (Brief, Page 9 and 17). It is agreed that *Merce-Vidal et al* "provides no hint as to moving the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring" as asserted by Appellant. However, Appellant's statement that *Merce-Vidal et al* "provides no hint as to moving the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring ***without losing affinity for the 5-HT_6 receptor***" (emphasis added) is somewhat misleading in that it suggests that *Merce-Vidal et al* considered moving the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring but concluded doing so would disrupt affinity for the 5-HT_6 receptor. This is certainly not evident anywhere in *Merce-Vidal et al*. Rather, *Merce-Vidal et al* are simply silent as to moving the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring. Despite this silence, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091 (Fed. Cir. 1986). In the instant case, as discussed above, it would have been obvious to move the amino moiety or the N-containing cycloaliphatic ring to the 1-position of the indole ring in view of *In re Wilder* and *Filla et al*. Appellant's statement to the contrary ("Neither would the skilled person have been motivated to change the $-(CH_2)_n-R^2$ moiety of *Merce-Vidal et al* to position 1 in view of the teaching of *Filla et al*" (Brief, Page 9)) without indicating more is acknowledged but not found persuasive.

As evidence that a position isomer based on a parent compound does not predictably retain the activity of the parent compound, Appellant points to examples in the prior art of compounds that would be considered position isomers of one another but which are disclosed as having different activities (Brief, Pages 17-19). For example, Appellant identifies compound (1) which is claimed as an inhibitor of thromboxane A2 synthesis, whereas its position isomer (i.e., compound (2)) is described elsewhere as a highly selective h5-HT1D receptor agonist (Brief, Page 17). Yet, as discussed in more detail in the previous Action, no where was compound (1) tested for activity as a h5-HT1D receptor agonist; nor was compound (2) tested for activity as an inhibitor of thromboxane A2 synthesis. That is, no where is it demonstrated that the activity of compound (1) is not also possessed by compound (2), and *vice versa*. Without this information, nothing at all can be taken from Appellant's evidence. It certainly can not be considered persuasive that "the skilled artisan would only readily understand from the referenced examples that positional isomers may show very different activities" (Brief, Page 19) since there is nothing to suggest that the positional isomers do, indeed, show very different activities.

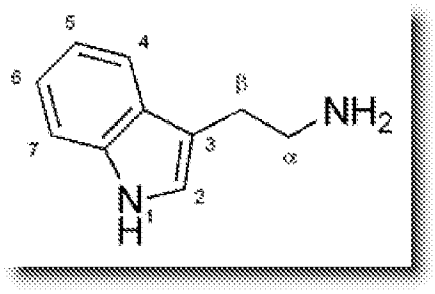
Appellant also argues that the change of the substituent from position 3 to position 1 results in two changes: (1) introduction of a substituent at position 1; and (2) disruption of the characteristic tryptamine-like structure at position 3 in *Merce-Vidal et al* (Brief, Pages 9-12). As to (1): as discussed above, the structurally and functionally related compounds of *Filla et al* (i.e., 5-HT_6 modulators possessing a substituted indole core) are substituted at position 1 of the indole core. Accordingly, the skilled artisan - who would ordinarily contemplate making isomers of the compound taught by *Merce-Vidal et al* to try to obtain compounds with improved properties (in view of *In re Wilder* (see also *Takeda* at page 1356)) - would consider ring-walking the moiety

to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT_6 modulators and possibly possess improved properties. Although it is accurate that that *Filla et al* (which discloses 5-HT_6 receptor modulators possessing an indole core which is substituted at position 1) does not contain the **exact** substituent at position 1 as is disclosed by the prior art compound taught by *Merce-Vidal et al* (wherein the substituent is located at position 3) and recited by the instant claims (as asserted by Appellant (Brief, Page 9 and 13-15)), *Filla et al* is applied as prior art in the instant rejection in that it indicates that substitution of the indole core at position 1 does not disrupt the compound's activity as a 5-HT_6 modulator. The fact that the compounds taught by *Filla et al* do not contain the **exact** substituent at position 1 (or elsewhere) as is taught in the instant claims would not dissuade the person of ordinary skill in the art from making the compounds since the skilled artisan would seek to ring-walk to the substituent taught by *Merce-Vidal et al* in the compound taught by *Merce-Vidal et al* to another position on the indole core of the compound taught by *Merce-Vidal et* capable of supporting a similar substituent and maintaining activity as a 5-HT_6 modulator. As such, as discussed above, the skilled artisan - who would ordinarily contemplate making isomers of the compound taught by *Merce-Vidal et al* to try to obtain compounds with improved properties - would consider ring-walking the moiety to position 1 of the indole core with the reasonable expectation that compounds possessing such modification would still function as 5-HT_6 modulators and possibly possess improved properties based on the disclosure of *Filla et al* which identify compounds having an indole core substituted at position 1 function as 5-HT_6 modulators.

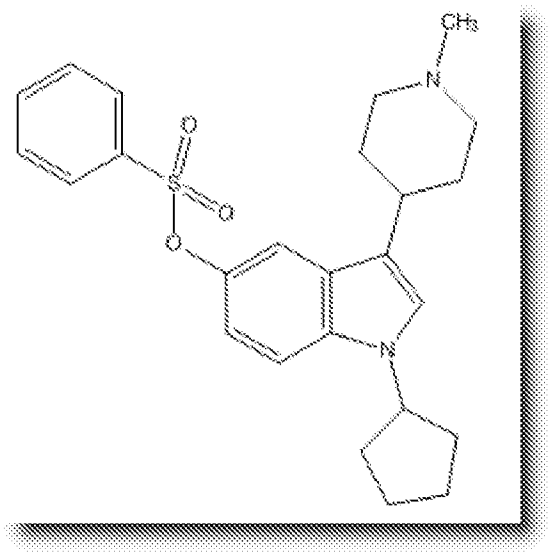
As to (2): Although Appellant argues that elimination of the substituent from position 3 disrupts the tryptamine-like structure, it is noted that Example 28 in *Filla et al*:



(Page 67) does not appear to possess a tryptamine-like structure any more than the instantly claimed compound possesses said structure; yet Example 28 is disclosed as a 5-HT_6 modulator. Thus, it is not found persuasive that the skilled artisan would have expected maintaining the tryptamine-like structure in the compounds taught by *Merce-Vidal et al* to be critical for their activity as 5-HT_6 modulators. **Tryptamine** is represented by the following structure



(tryptamine) whereas

Example 28 has the following structure  (Example 28). As such, Example 28 possesses a 3-amino**cycloalkyl**indole structure, but not a 3-amino**alkyl**indole basic structure. Furthermore, whereas the amine group in tryptamine is a primary amine, the amine in Example 28 is a tertiary amine. In view of these two differences, it is not found persuasive that Example 28 possess a tryptamine-like structure or that the skilled artisan would have expected maintaining the tryptamine-like structure in the compounds taught by *Merce-Vidal et al* to be critical for their activity as 5-HT_6 modulators.

Appellant, however, further argues that other prior art references identify compounds, which are tertiary amines, specifically as "tryptamine analogues" (Brief, Page 12). However, it is also noted that the prior art references cited by Appellant do not identify 3-amino**cycloalkyl**indole structures as tryptamine analogues. Nevertheless, the genus of compounds encompassed by "tryptamine analogues" is considered significantly broader than the genus of compounds encompassed by "tryptamine-like". Thus, the fact that a compound is identified as a "typtamine analog" does not necessarily entail that the compound is also a "tryptamine-like" compound.

Appellant additionally argues that the Final Office Action is mainly aimed to differentiate the instant case from *Takeda* (Brief, Page 8). Indeed, as discussed in detail in the Final Office Action mailed October 1, 2009, the fact pattern of the instant case is significantly different from that of *Takeda*. As noted in that Office Action, in *Takeda*, the structurally related prior art compound species (which was modified to provide the alleged *prima facie* obvious compound) was disclosed as possessing certain disadvantageous properties (i.e., toxicity). Yet, in *Takeda*, the modification of the structurally related prior art compound species (which was disclosed as possessing certain disadvantageous properties (i.e., toxicity)) unexpectedly resulted in a compound lacking the toxicity of the structurally related prior art compound. In the instant case, however, there is nothing to suggest that the prior art compounds taught by *Merce-Vidal et al* (which were, significantly, listed among only 53 total compounds) exhibited any disadvantageous properties that would have taught the skilled artisan not to select that compound for modification. Furthermore, in the instant case, there is no evidence of unexpected results attributed to the modification of the compounds taught by *Merce-Vidal et al* in view of *In re Wilder* and *Filla et al.* Although the Brief contains a section titled "Unexpectedly superior results over the prior art" (Page 15), Appellant does not indicate any such results.

As also discussed in detail in the Final Office Action mailed October 1, 2009, the fact pattern of the instant case is significantly different from that of *Takeda* in that there is no evidence that at the time the instant invention was made, ring walking was not a routine step in the drug optimization process, as was the case in *Takeda*. Appellant, however, argues that ring walking does not represent a routine step in the drug optimization process since there is nothing in the prior art to suggest performing said ring walking (Brief, Pages 12-13). This is not found to

be persuasive since *In re Wilder* – which specifically teaches that: "[c]ompounds which are position isomers (compounds having the same radicals in physically different positions on the same nucleus)… are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties" – thus suggests ring walking.

For at least the above reasons, it is apparent that the rejections are proper within the meaning of U.S.C. 103, and render the claimed invention is obvious.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/CRAIG RICCI/

Examiner, Art Unit 1628

Conferees:

/Brandon J Fetterolf/

Supervisory Patent Examiner, Art Unit 1628

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627